systemic delivery of the active ingredient having a solvent film forming agent and cellulose and a plasticizing agent. The Examiner concedes that the primary references do not teach the use of the preferred carrier materials of propyleneglycol and the like and that they do not teach the weight ratio of nomegesterol to be 0.05 to 1% by weight and do not teach the specific ratios. The Examiner cites the Eibl et al patent as teaching propyleneglycol and copolymers of methyl acrylic acid and ethylacrylate as being auxiliary agents for pharmaceuticals and topical formulation. The Merck Index is cited to show that isopropylpropilidene glycerol may be used as the plasticizing agent and the Remington references teaches that carbomer is useful as a gelling and emulsifying agent and deems that the compositions would be obvious.

Applicants respectfully traverse these grounds of rejection since one skilled in the art would not combine the prior art without the benefit of Applicants' disclosure. The present invention is drawn to a topical hormonal composition having a systemic effect for the correction of progesterone deficiency in premenopausal women and for hormone replacement is menopausal women containing as the active ingredient nomegesterol and esters and ethers thereof, a vehicle permitting systemic passage of the active ingredient selected from the group consisting of a solubilizing agent and an absorption promoter, a film forming agent and a gelling agent or mixtures thereof combined with a suitable excipient for the production of a gelled or film forming

pharmaceutical. Applicants' compositions are not for topical use but are for systemic use.

As noted previously, the Saunal et al patent relates to a composition for transdermal delivery of an active ingredient which could be nomegesterol acetate and optionally a polymeric release matrix capable of forming a flexible film when dried which matrix is selected from cellulose polymers or copolymers and vinylpyrrolidene, vinyl acetate copolymers and a physiologically non-aqueous solvent to dissolve the release matrix and the transcutaneous absorption promoter by quickly removing the same by evaporation from the skin.

A transdermal composition is completely different from a gel with systemic activity. Transdermal compositions are made of a small reservoir fixed to a strip of plastic material and the reservoir is faced to the skin. The reservoir usually contains a large amount of an active ingredient dissolved in a lipophilic dileunt and the active ingredient diffuses to the skin from the lipophilic phase to pass through the skin. The objective of such a preparation is to have a delayed or protracted diffusion of the active ingredient through the skin. A transdermal device is not intended to have the product reach the bloodstream but is intended to diffuse the active ingredient from the reservoir through the skin. The compounds present in the reservoir are selected due to their high lipophilicity and includes compounds such estradiol,

scopolamine, nicotine and the like.

Applicants' formulation has absolutely nothing to do with a transdermal application since the purpose of Applicants' invention is to insure optimum passage of the active principal nomegesterol through the skin and into the bloodstream. Therefore, the Saunal et al patent in no way relates to Applicants' invention.

The Winters et al patent is directed to a topical polymeric drug delivery system for delivering drugs to the skin topically involving the use of a propellant free airless pump for the delivery and this has absolutely nothing to do with Applicants' invention.

Synthetic progesterones have the main drawback of having very poor diffusion properties through the skin due to their lipophilic character and Applicants' invention provides a precise balance between the solubility of the active ingredient and the vehicle and its ability to diffuse through the skin towards the bloodstream. This is why the mixture proportion of the preferred solubilizing agent suitable for Applicants' invention is the main point of distinction with respect to the prior art. The effectiveness of the composition is the result of the proper combination and term of dosage of all the excipients.

In Applicants' invention, the preferred solubilizing agent is

a ternary mixture or a quaternary mixture of 95% ethanol/water/propyleneglycol and optionally Labrasol wherein the percentage of 95% ethanol varies from 30 to 50% and the amount of water is 30 to 60% and the propyleneglycol is 2 to 20% and the Labrasol is 3 to 7%, all percentages being by weight. This composition permits nomegesterol to pass through the cutaneous barrier to obtain good clinical results when the excipient mixture proportions are properly balanced as can be seen from the examples in the application as filed.

The Saunal et al compositions do not contain propylene glycol which contributes to the effectiveness of the diffusion through the skin and Saunal et al did not show any examples of compositions containing 19-nor progesterone derivatives and specifically not nomegesterol acetate. The reference taught estradiol compositions as being easily obtained and satisfactorily efficient due to the high lipophilicity of estradiol. Saunal et al only postulates the possibility that these compositions could contain nomegesterol acetate and does not teach Applicants' advantages of the compositions. There is no way to obtain Applicants' gel having systemic activity with the active ingredients being highly lipophilic. Therefore, the combination of the prior art does not teach Applicants' invention and withdrawal of these grounds of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosures

MARKED UP VERSION OF CLAIMS

Claim 11 (twice amended) A topical hormonal composition with systemic effect of claim 1 containing a gelling agent selected from the group consisting of cellulose derivatives selected from the group consisting of

methylcelluloses,

ethylcelluloses (Ethocel),

hydroxypropylmethylcelluloses,

hydroxyethylcelluloses,

hydroxypropylcelluloses and

carboxymethylcellyloses in the sodium or calcium form

and acrylic [derivatives] carbomer.

Claim 14 (twice amended) A topical hormonal composition with systemic effect of claim 1 containing a film-forming agent selected from the group consisting of cellulose [derivatives], acrylic, methacrylic acid [derivatives] copolymers and polyvinylpyrrolidone [derivatives].